REMARKS

The Applicant thanks the Examiner for timely indication that claims drawn to lactose are apparently free of the prior art. Reconsideration of the present application in view of the following discussion and remarks is respectfully requested.

The Office bears the initial burden of factually supporting a *prima facie* case of anticipation. As stated by the Federal Circuit, "[a]nticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." Lindemann Maschinenfabrick GmbH v. American Hoist & Derrick Co., 730 F.2d. 1452, 221 USPQ 481, 485 (Fed. Cir., 1984) (citing Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983).

The Federal Circuit has also stated that that, "An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 20 USPQ 2d. 1746, 1749 (Fed. Cir. 1991).

Chen does not disclose every element of the Applicant's invention therefore the rejection of claims 1, 2, 5, 11 and 14 under 35 U.S.C. § 102(a) over Chen should be withdrawn and claims 1, 2, 5, 11 and 14 should be allowed.

Claim 1, the only independent claim of the instant Application recites:

"A pharmaceutical composition comprising:

a single crystal of a pharmaceutically acceptable crystal lattice componet, and

an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation the crystal lattice component and the active pharmaceutical ingredient being pharmaceutically pure". Application, claim 1.

The Applicant's Invention, unlike the Chen reference is not limited to co-crystallization of an API with a sugar compound.

The Office Action states that Chen, "discloses the co-crystallization of an API with sucrose". Office Action, pg. 3. As evident from the text of claim 1 (cited above) the instant Application does not recite that the active pharmaceutical ingredient (API) is incorporated into "a single crystal" is necessarily itself a crystal. See Application, claim 1. Accordingly the co-crystallization process disclosed by Chen does not anticipate the Applicant's claimed invention. As Chen by does not teach all of the elements of the Applicant's invention the Applicant respectfully requests that the rejection of claims 1, 2, 5, 11 and 14 under 35 U.S.C. § 102(a) be withdrawn and that all pending claims be allowed.

The Applicant's Invention, unlike the Chen reference is not directed to an active ingredient incorporated as an integral part of the a sugar matrix.

The Action asserts that the product of the Chen reference anticipates the Applicant's invention because the reference teaches that "the active ingredient is incorporated as an integral part of the sugar matrix." Action, pg. 3 citing to Chen pg. 8. However, the APIs and biopharmaceuticals in the Applicant's invention are not 'integral to the crystal'. As stated clearly in Applicant's claim 1, " an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation ..." Application, claim 1. Since Chen teaches an ingredient that is integral to a sugar crystal lattice while the Applicant claims an API is a specific orientation within the crystal the reference and the Application recite products with different structures. Since the structures of the products are different Chen does not anticipate the Applicant's invention. Accordingly, the Applicant respectfully requests that the rejection of claims 1, be withdraw and that claim 1 be allowed. As independent claim 1 is allowable the Applicant respectfully requests that claims 2, 5, 11 and 14, which depend from claim 1 be allowed.

The methods recited in Chen will not make the product claimed by the Applicant, therefore Chen does not anticipate the Applicant's invention.

The Action concedes that "The reference [Chen] is silent with regard to the API being included in the crystal in a growth-sector specific orientation." Action pg. 3. However, the Examiner goes on to conclude that the product prepared in Chen "inherently comprises the required limitations". Action, pg. 3. The Action goes on to recite that, "The produce is prepared from a saturated solution in a manner similar to the

inventive product, and the reference [Chen] teaches, "that the active ingredient is incorporated as an integral part of the sugar matrix"". Action, pg. 3. In summary the Action asserts that the methods disclosed by Chen and those disclosed by the Applicant are so similar that they will produce the same product. To support this inference the Action cites examples 7-9 and 13 and page 8 of Chen. See Action, pg. 3.

The assertion methods for forming a product disclosed in Chen and in the instant Application are so similar that they form the same product is incorrect. In actuality the conditions for product formation disclosed by Chen are markedly different from the conditions for product formation recited in the instant Application. Accordingly, the methods taught by Chen will not produce the product claimed by the Applicant.

The methods disclosed by Chen use high temperatures, vigorous mixing and quick crystallization all steps known in the art to destabilize many APIs and most biopharmaceuticals. See for example page 8a of Chen, which recites three examples that incorporate a premixing step and mixing the premixed with a saturated sugar solution at temperatures in excess of 270°F. Examples 7, 8, 9 and 13 of Chen teach 'premixing' a compound with sugar before adding the heated, supersaturated sugar solution. See Chen example 7, pg. 11; example 8, pg. 12; example 9, pg. 12; and example 13 pg. 14. Examples 7, 8, 9, and 13 of Chen all teach mechanical mixing or impact beating of the sugar syrup dry sugar compound premix.

Example 7, 8 and 13 of Chen all disclose adding a compound to, " ... a heated, superheated sugar syrup, prepared as in Example 1". See Chen example 7, pg. 11; example 8, pg. 12; example 9, pg. 12 and example 13 pg. 14. Example 1 of Chen, referenced by examples 7, 8, 9 and 13 discloses method for preparing and adding an

ingredient to a supersaturated, hot syrup at a temperature of 260° F. See Chen pg. 9. Example 9 of Chen recites nine enzymes of largely industrial utility and states, "Notwithstanding the high temperature of the process the enzyme remains in its active form". Chen, pg. 13. This example does not proffer any quantitative data showing exactly how active these enzymes are nor does it show any figures indicating that the enzymes are orientated in the growth-sector specific portion of a crystal.

Specific examples of the methods for product formation taught by Chen are as follows. Example 7, of Chen recites in part:

> "10 grams of Vitamin A palmitate ... was admixed with 390 grams of transformed sugar ... . 600 grams of a heated, supersaturated sugar syrup, prepared as in Example 1, was added to the premix with mechanical agitation. Stirring was continued until the sugar was transformed and the agglomerated into a dry product." Chen, pgs. 11-12.

Example 8, of Chen recites in part:

> "2.08 grams of stannous fluoride was mixes with 297.92 grams of transformed sugar ... to form a premix 600 grams of a heated supersaturated sugar syrup, prepared as in Example 1, was added to the premix with impact beating. Impact beating was continued and crystallization proceeded, eventually resulting in the formation of a dry powered product." Chen, pg. 12.

Example 9 of Chen recites in part:

> "Example 8 was repeated except that 100 grams of ferrous sulfate was blended with 300 grams of sugar to form the premix.
>
> In another embodiment, a dry enzyme product of an active culture is produced by incorporating an enzyme, such as invertase, cellulase, glucose, isomerase, amylase, catalase, glucose oxidase, lactase or pecitanase, or an active culture into a sugar matrix. Chen pg. 12.

Example 13 of Chen recites in part:

> "100 grams of lecithin (Centophase C, Central Soya) was mixed with 200 grams of granular sugar (Bakers Special Grade) to form a premix. 800 grams of a heated, supersaturated sugar syrup, prepared as in Example 1, was added to the premix with impact beating. Impact beating was continued and crystallization

proceeded, eventually resulting in the formation of a dry powdered product. Chen, pg. 15.

Example 1 of Chen, cited either directly or indirectly in Examples 7-9 and 13 recites, in part, as follows:

> "At the same time, 700 grams of a 65° Brix sugar solution was concentrated at 260°F to 95 % by weight solids content." Chen, pg. 9.

In contrast the Application recites product formation conditions that are markedly gentler than the conditions disclosed by Chen. This is clearly illustrated, for example, on page 69 of the Application, which recites as follows:

> "Typical crystal growth conditions involved the additions of 1 volume of an approximately 10 mg/mL *rhodamine- or Texas red-labeled peptide or proteins in a 0.1-M phosphate-buffered saline solution (PBS, pH7.4) to* 10 volumes of a supersaturated a-lactose solution or phthalic acid solution. Supersaturated solutions of purified a-lactose were obtained by adding 0.41 grams of α-lactose to 1 mL of purified water, allowing to dissolve in 50-70°C water bath and *cooling to room temperature.* Supersaturated solutions of phthalic acid were prepared by adding 0.05 grams of phthalic acid to 1 mL of either 70/30 (v/v) water/acetonitrile or 90/10 water/ethanol, allowing to dissolve in a 50-70°C water bath and cooling to room temperature. Larger volumes of supersaturated solutions are obtained by using the same solute-to-solvent ratio.
>
> The *solutions of labeled peptide with the supersaturated a-lactose or phthalic acid were mixed by swirling, transferred to a 24-well crystallization plate* or other suitable glass or polypropylene contained, and *allowed to stand at room temperature, Crystals were harvested in 4-5 days and rinsed with hexanes, ethanol, or methanol.*" Application pg. 69, Italics added for emphasis.

The instant Application also provides data, illustrating that Green Fluorescent Protein (GPF) over grown with crystalline α-lactose monohydrate is as active as GPF in a saturated solution of α -lactose. See Application, pg.67; and Figure 1. The instant Application also shows that the GFP α-lactose product of the instant Application made in accordance with some of the methods disclosed in the Application is "localized with in

sharply defined pyramid corresponding to the (010) growth sector". See Application, pg. 67 and Figure 2.

As illustrated by this example the methods disclosed in the instant Application are distinct from the method disclosed in Chen. Accordingly the products produced by the methods disclosed in the instant Application are distinct from the products made using the methods disclosed by Chen.

The general methods disclosed by Chen were characterized in the 'Background Section 'of the instant Application. See Application, pgs. 3-6. A portion of this section may help to distinguish some embodiments of the Applicant's invention from products made by methods similar to the methods disclosed in Chen, for example, the instant Application recites as follows:

> "Other prior art procedures have required the use of polymers that are difficult to prepare, require harsh preparations conditions that can be harmful to the API's and yield inconsistent results. For example, United States Patent No. 5,075,291 describes a process for preparing a uniformly –dispersed pharmaceutically-active material in a crystalline sugar alcohol matrix. However this process requires the addition of the API into a molten sugar alcohol with considerable mechanical agitation. Many API's and virtually all biopharmaceuticals would not be stable in the extreme temperature of 110°C and the physical stress of a high-shear vortex mixer used for agitation. The present invention does not require these extremes of temperature and physical agitation. Also, the process of the present invention slowly includes the API into the growing crystal lattice in specific growth sections, instead of homogenous mixing and entrapping of the active pharmaceutical ingredient in viscous melt. Application, pgs. 5-6.

While the process recited in this section is not exactly analogous to the process disclosed in Chen it clearly teaches the harmful effects of extreme temperature and physical stress, as disclosed in Chen on API's and biopharmaceuticals. Accordingly, the methods disclosed by Chen will not produce the products of the claimed invention.

Furthermore those of ordinary skill in the art would recognize that many steps of the process disclosed by Chen would alter the chemical and/or physical structure of many if not most of the API's and biopharmaceuticals disclosed in the Application. See Application, Table A, pgs. 18-55.

The methods taught by Chen do not teach or suggest a method of producing the Applicant's claimed invention " an active pharmaceutical ingredient different from and included within the crystal in a growth-sector specific orientation". See Application, claim 1. Accordingly the disclosure of Chen does not anticipate the Applicant's invention and the rejection of claims 1- based on 35 USC § 102(b) should be withdrawn and claims should be allowed.

Claims 1-6 and 11-14 are not obvious over the Chen and the Applicant respectfully requests that the rejection of claims 1-6 and 11-14 under 35 U.S.C. 103(a) in view of Chen be withdrawn and that claims 1-6 and 11-14 be allowed.

The Action asserts that example 10 of Chen teaches that an active form of the enzyme invertase can be included in a sugar matrix using the methods taught by Chen and that example 10 of Chen makes obvious the Applicant's claims. See Action pg. 5. This is incorrect, example 10 of Chen teaches premixing the invertase with sugar and next adding "a hot supersaturated sugar syrup" and that, "agitation was continued until the sugar was transformed, crystallized and agglomerated". See Chen, pg. 13.

Example 10 of Chen states that " in spite of the high temperature used in the process, the experimental results indicate that a significant portion of the invertase

remained active." Chen pg. 13. However, Chen does not indicate exactly what portion of the enzyme is active. And Chen does not show images of invertase within the "the crystal in growth-sector specific orientation" as claimed by the Applicant. Application claim 1; Fig. 2. Again as discussed in the above, the method taught in Example 10 of Chen is too harsh to produce the product claimed by the Applicant, "a single crystal of a pharmaceutically acceptable crystal lattice component and an active pharmaceutical ingredient different from and included with the crystal in a growth-sector specific orientation . .. ". Application claim 1. Accordingly, the Applicant respectfully requests that the rejection of independent claim 1, as being obvious over Chen be removed and that claim 1 be allowed. As claim 1 is allowable so too are dependent claims 2-6 and11-14, which depend from claim 1, accordingly the Applicant respectfully requests that the rejection of claims 1-6 and 11-14 be removed and that claims 1-6 and 11-14 be allowed.

In view of the foregoing, it is respectfully submitted that claims 1-6 and 11-14 are in condition for allowance. Reconsideration of the instant Application in view of the foregoing is respectfully requested. The Examiner is encouraged to contact the undersigned by telephone to resolve any outstanding matters concerning the instant Application.

Respectfully submitted,

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